**Background, Treatment and Management in a Patient with Bilateral Choroidal Metastases**

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**Abstract**

Choroidal metastasis refers to a tumor that stems from a primary malignancy elsewhere in the body and spreads to the choroid through blood circulation. While once considered rare, choroidal metastasis is now considered the most common adult intraocular malignancy. Due to advances in treatments, extended life expectancy in those diagnosed with cancer has increased the prevalence of choroidal metastasis. Along with ultrasound and fluorescein angiography, newer ocular imaging techniques are clinically accessible to aid in the diagnosis and management of the tumors. Different treatment strategies are also available to best suit the patient’s systemic and ocular states. This case report reviews the background, treatment and management of a patient with choroidal metastases.

**Keywords**: Choroidal metastasis, Choroidal melanoma, Optical Coherence Tomography, Anti-vascular endothelial growth factor injection

**Introduction**

The choroid, with its rich vascular supply, is the most common site for intraocular metastasis, accounting for 90% of uveal tumors. The first case of choroidal metastasis was documented in 1872 and was previously considered an uncommon finding, but it is now recognized as the most common adult intraocular malignancy. Choroidal metastasis is likely clinically underdiagnosed, typically becoming apparent later in the course of malignancy in ailing patients, but autopsy studies of patients who died of cancer have shown a higher prevalence of choroidal metastasis.

Given that choroidal metastasis occurs at a higher rate than previously believed, potentially even as the first sign of cancer, eye care practitioners can have an important role in the diagnosis and management of the disease. Understanding its clinical manifestations and treatment modalities will help to better inform the patients. With new advances in cancer treatment, life expectancy has improved significantly, so the importance of visual function on the patient’s quality of life cannot be overlooked.

**Case History**

A 61-year-old Caucasian male presented to the optometry department with a chief complaint of loss of vision in the right eye for six weeks. The patient was diagnosed with lung cancer five months prior at another facility, but chose to forego medical treatment, opting for homeopathic remedies instead, and had not been evaluated by a medical professional since the date of diagnosis. Visual acuity measured hand-motion in the right eye (OD) and 20/20 in the left eye (OS). Confrontation visual fields showed hand motion in all four quadrants OD and full to finger counting OS. Extraocular muscles were full and unrestricted both eyes (OU). Anterior segment findings were within normal limits OU. Goldmann applanation tonometry measured 10mmHg OD and 12 mmHg OS. Dilated fundoscopic evaluation showed bilateral elevated retinal lesions with chorioretinal pigmentary changes, measuring approximately 4x4 disc diameters OD and 2.5 x 2.5 disc diameters OS (see Fig. 1). Optical Coherence Tomography (OCT) revealed elevated lesions with subretinal fluid OU, with leakage into the macula OD (see Fig. 2 and Fig. 3). Following the exam, the patient was referred to a retinal specialist to confirm suspicion of choroidal metastases as well as to his primary care provider for a full systemic work up for metastasis.

A retinal specialist examined the patient two days later, confirming bilateral choroidal metastases. As a result, chemotherapy was recommended to reduce the burden of the tumor as well as to expedite resolution of sub-retinal fluid. However, the patient adamantly refused chemotherapy insisting on local treatment only. The patient agreed to intraocular injections to treat the tumor in hopes of restoring vision OD.

One week later, the patient underwent an Avastin (bevacizumab; Genentech, Inc.; South San Francisco, CA) injection OD. The plan was for a series of three Avastin injections every four weeks. If a good response was noted OD or if vision decreased OS, treatment would be initiated OS as well.
Systemically, the patient completed a Positron Emission Tomography (PET) scan and a chest X-ray (see Fig. 4), which showed large lung opacities that occupied almost the entire left lung with intense fluorodeoxyglucose (FDG) uptake, consistent with malignancy. The PET scan also revealed multiple bone metastases including bilateral ribs, spine, right humeral head, and bilateral iliac bones. Despite these findings, the patient continued to refuse all systemic treatment options. The patient’s condition worsened significantly, and he was admitted to hospice care one month later. Following admission, he was unable to complete the series of Avastin injections. The patient eventually passed away three months after his initial visit to the optometry department.

Discussion
The most common site of origin for choroidal metastases is breast cancer in women and lung cancer in men. Roughly 25% of patients who present to eye care providers with a metastasis have no known history of systemic cancer. Furthermore, approximately 10% of patients with choroidal metastases have no detectable primary cancer after a full systemic work up, in which case a biopsy may be indicated.

In a review of 479 eyes with a choroidal metastasis, the most common presenting symptoms of choroidal metastases are blurred vision, followed by flashes and floaters, and lastly, pain. However, about 10% of patients are asymptomatic, in whom metastases may be incidentally detected on routine exam. The most common clinical presentation was a yellow subretinal mass (94%) with associated subretinal fluid in 74% of cases. Uncommonly, a choroidal metastasis presented as brown-gray (3%) or orange in color (3%). Lesions are typically located posterior to the equator, often involving the macula. The mean number of tumors per eye was 1.6. Bilateral and multifocal metastases were more frequently associated with breast cancer, while unilateral lesions were more often linked with lung cancer.

Imaging Characteristics
In addition to fundoscopy, ancillary imaging may be helpful in confirming choroidal metastasis, differentiating it from other choroidal conditions. This may include ultrasonography, fluorescein angiography, optical coherence tomography, and fundus autofluorescence.

In a patient without previous history of cancer diagnosis, ultrasonography may be helpful in differentiating metastasis versus other amelanotic tumors. Ultrasonography uses high-frequency soundwaves to provide detailed images of the structures of the eye and orbit. The A-mode of ultrasonography provides information about the axial length of the eye and can also be used to determine the size of mass. The B-mode provides a cross sectional view of the eye and orbit. Sobottaka and Kreissing found that choroidal metastases showed an increase in reflectivity and a decrease in height-to-base ratio, allowing for differentiation between choroidal melanomas and metastases. Additionally, ultrasonography may be used to track the effectiveness of treatment in relation to tumor regression or growth.

Fluorescein angiography is a test in which dye is injected into the bloodstream to highlight blood flow changes in the retina. Each retinal disease displays a characteristic pattern of changes, which allows for insight on diagnosis and treatment. In choroidal metastasis, fluorescein angiography will show hyperfluorescence of the mass in the late venous stage, which occurs later than with choroidal melanoma or hemanigoma. Pinpoint leakage at the tumor border also has been shown to be a diagnostic factor, occurring in roughly 74% of metastatic lesions versus only 16% of choroidal melanomas.
Optical coherence tomography (OCT) is a noninvasive cross-sectional diagnostic imaging device, which allows for visualization of the retinal tissue microstructure. In recent years, two advances in OCT imaging have allowed for better resolution when viewing the choroid. These advances include enhanced depth imaging (EDI-OCT) and optical coherence tomography angiography (OCT-A).

EDI-OCT provides increased resolution of the deeper layers of the choroid and sclera. Prior to EDI-OCT, spectral-domain OCTs had difficulty imaging deeper structures. This ability to image the choroid with increased resolution has allowed for the ability to measure tumor size and delineate clinical characteristics of the tumor. It is especially beneficial in detecting small tumors, sometimes before they are clinically apparent. Demirci et al. used EDI-OCT to determine features of choroidal metastases and their corresponding changes following treatment. The most common features found by EDI-OCT of choroidal metastases include: shaggy photoreceptors (79%), subretinal fluid with speckles (75%), thinning of the choriocapillaris over the tumor (100%) and plateau-shaped tumor elevation (75%). In addition, following treatment there was an increase in high internal optical reflectivity, consistent with more tissue fibrosis.

In OCT-A, rapid repeated B-scans taken at the same position are compared to provide information regarding blood flow. A study done by Toledo et al. described OCT-A findings in 79 various chorioretinal tumors in order to correlate risk factors for growth. While the study mainly looked at melanocytic tumors (choroidal nevi and choroidal melanomas), one case of a choroidal metastasis was included in the study. The OCTA of the choroidal metastasis was described as a “very disorganized choroidal plexus with anastomosis, thick and fine vessels, large avascular zones, and vascular loops.” These advances in OCT imaging are important as increased visualization of the choroid allows for better diagnosis and the ability to easily follow treatment response.

Like OCT, fundus autofluorescence (FAF) is a non-invasive imaging technique, which provides information of macular diseases and tumors. FAF has been shown to accentuate certain physiological features. In conditions where the retinal pigment epithelium (RPE) has been damaged with excess retinal lipofuscin, subretinal fluid, and drusen characteristic areas of hyperautofluorescence are observed. Contrarily, disease processes which lead to photoreceptor cell death will show areas of hypoautofluorescence. A study completed by Natesh et al. looked at ten choroidal metastases and their characteristic FAF properties; it was found that FAF best defined surface characteristics and tumor margins, showing an intense hyperautofluorescence of surface pigmentation and a diffuse hyperautofluorescence in areas with subretinal fluid. Furthermore, tumor margins showed hypoautofluorescence or isoautofluorescence.

In cases where a diagnosis or a primary source of metastasis cannot be determined, fine needle aspiration biopsy can be performed. Shields et al. found fine needle aspiration to be a safe and reliable diagnostic method; however, the technique should be reserved for cases in which there is diagnostic uncertainty due to the invasive nature of the procedure.
**Differential Diagnoses**

It is important to delineate choroidal metastases from other conditions that may mimic the disease, especially in a patient with no known history of cancer diagnosis. Differential diagnoses for choroidal metastases include choroidal melanoma, sclerochoroidal calcification, choroidal osteoma, and solitary idiopathic choroiditis.

A choroidal metastasis can often be mistaken for a choroidal melanoma. While both are tumors of the choroid, choroidal melanomas are primary tumors meaning they originate from the choroid. Conversely, metastasis refers to a tumor that stems from a primary malignancy elsewhere in the body and spreads to the choroid. To aid in diagnosis, previously discussed ancillary tests are helpful, especially ultrasonography, as they demonstrate different imaging characteristics. On ultrasonography, choroidal melanomas will show decreased reflectivity, higher height-to-base ratio, and choroidal excavation.2,13

Sclerochoroidal calcification presents as multiple yellow placoid lesions, most often bilaterally and in the superotemporal region posterior to the equator. Sclerochoroidal calcification is usually idiopathic but has been linked to systemic conditions with impaired calcium phosphorous metabolism and renal tubular hypokalemic metabolic alkalosis syndromes.14 On ultrasound, sclerochoroidal calcification have high reflectivity with acoustic shadowing posterior to the lesion.15

Choroidal Osteoma is a benign ossifying tumor, which predominantly affects young females in their second decade of life. It is considered rare and the exact etiology is unknown. The condition often presents unilaterally in the juxtapapillary and macular regions of the retina. In the earlier stages of the disease process, choroidal osteomas appear orange-red in color. Later in the disease process as atrophy to the overlying RPE occurs, lesions will appear yellow-white, mimicking the appearance of a choroidal metastasis.16,17 EDI-OCT is especially helpful in differentiating choroidal osteomas from choroidal metastases. Choroidal osteomas will display hyper-reflective horizontal lamellar lines, representing lamellae of bone, a unique feature not observed in other choroidal tumors.18

Solitary idiopathic choroiditis (SIC) is an isolated inflammatory choroidal lesion of unknown etiology even after extensive systemic evaluation. It can have a similar clinical appearance to choroidal granulomas that are associated with a variety of diseases, including sarcoidosis and tuberculosis, but SIC tends to present with a lesser degree of inflammation. In the inactive stage, SIC appears as distinct, round or oval, yellow white lesions, often surrounded by an ill-defined red-orange halo. In the active stage, it appears as indistinct, dull yellow lesions with exudation, subretinal fluid, vascular dilation, and focal hemorrhages. FA shows early hypofluorescence with late hyperfluorescence, more intense than that of choroidal metastases.19 FAF tends to be homogenously hyperautofluorescent, in contrast to the hyper- and hypo-autofluorescence of choroidal metastases.20

**Treatment/Management**

Ocular metastasis treatment aims to prevent vision loss and eye pain in order to improve the patient's quality of life. The treatment approach of choroidal metastasis depends on multiple factors including: overall status of systemic condition, visual symptoms, location, laterality, and number of lesions. For patients with bilateral or multifocal metastases, systemic chemotherapy, hormone therapy, immunotherapy or whole eye radiation (external beam radiation therapy - EBRT) is the preferred treatment method. For unilateral and solitary tumors local therapy such as plaque therapy, photodynamic therapy (PDT), or transpupillary thermotherapy (TTT) is advised. Lastly, in a patient with poor systemic prognosis, simple observation is recommended.21

Systemic chemotherapy, hormone therapy or immunotherapy is the preferred method of treatment for bilateral metastases. This is because the choroid is external to the blood ocular barrier, allowing systemic medications to freely diffuse into the choroid through the fenestrated endothelium of the choriocapillaris. Additionally, use of systemic medications reduces risks for toxic complications from radiation therapies as discussed below. Systemic therapy alone has been shown to regress tumors in patients with breast and lung cancer with good success.22-24

External beam radiation therapy delivers high-energy x-rays generated from an external machine aimed at the tumor to destroy cancerous cells. In a retrospective study on use of EBRT for treatment of choroidal metastases, 46% of patients showed an improvement in ocular symptoms while the remaining 54% of patients showed stability of symptoms. No visual degradation was found with use of EBRT.25 Despite its widespread use, treatment is not without local ocular side effects including cataract formation, radiation retinopathy, radiation optic neuropathy, exposure keratopathy, and iris neovascularization amongst others.25-27 Unfortunately, multiple treatment sessions are required as the total dose needed to kill a tumor is too toxic to be given in one session, which may prove problematic given the majority of patients with advanced disease states.

Plaque therapy allows for more focal delivery of radiation treatment to the lesion site. With plaque therapy, a small thin plate with radioactive seeds is surgically sewn onto the eye, covering the base of the tumor. Radiation is delivered over a period of several days and then removed upon completion of treatment. In a study completed by Shields et al. plaque therapy was found to be effective, showing tumor regression in 94% of patients over a mean follow up of 11 months. Although the focal delivery method decreases ocular side effects, some radiation complications can still occur.28

Photodynamic therapy was previously popular for the treatment of choroidal neovascularization. PDT works by targeting and destroying tumor cells via singlet oxygen. Singlet oxygen is a highly reactive oxygen species, which also leads
to tumor vascular damage and triggers an immune response against tumor cells.\textsuperscript{29} PDT with verteporfin, which specifically targets vascular endothelial cells, has been used to reduce choroidal tumor size secondary to metastasis.\textsuperscript{30} Additionally, Ghodasra et al. also found that more than two thirds of patients showed improved or stable acuity following treatment with PDT. Resolution of subretinal fluid was found in 86% of patients, as well as 81% of tumors were flat on ultrasound.\textsuperscript{31}

Transpupillary thermotherapy, a treatment method for choroidal melanomas and choroidal hemangiomas, has now been shown to effectively treat choroidal metastases. In TTT, an infrared diode laser administers heat to the choroid to shrink and kill cancerous cells. A study of 59 eyes with choroidal metastasis at the posterior pole showed tumor regression or inhibition of growth in 71% of patients.\textsuperscript{32}

Intravitreal antivascular endothelial growth factor (anti-VEGF) injections are still in the experimental stages for treatment of choroidal metastases and are currently being used off-label. Anti-VEGF inhibits new blood vessel formation and vascular leakage. Choroidal metastases require neovascularization for growth. Hence by inhibiting angiogenesis, ideally regression of tumor and subretinal fluid should occur. While only a small amount of clinical cases has been reported, many have presented good success with bevacizumab, showing shrinkage in choroidal mass.\textsuperscript{26,33,34}

**Conclusion**

With newer advances in treatments, life expectancy in those diagnosed with cancer has increased. Along with expanded life expectancy is the increased potential for encountering choroidal metastases in daily practice. Eye care practitioners need to familiarize themselves with the condition, as choroidal metastases can be the initial presentation of cancer and carries a high risk of mortality. It is imperative to properly diagnose the disease and make the appropriate referrals to retinal and oncology specialties so work up and treatment can be promptly implemented.

**References**


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